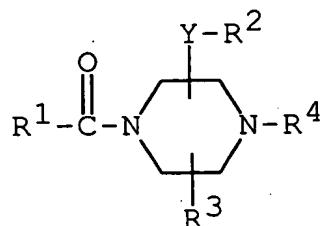


## C L A I M S

## 1. A compound of the formula :

5



10

wherein

Y is bond or lower alkylene,

R¹ is aryl which may have substituent(s),

R² is aryl or indolyl, each of which may have  
15 substituent(s),

R³ is hydrogen or lower alkyl;

R⁴ is pyridyl(lower)alkylamino(lower)alkynyl;

N-(lower alkyl)-N-[pyridyl(lower)alkyl]amino-  
(lower)alkyl;

hydroxy(lower)alkoxy(lower)alkyl;

lower alkanoyl(lower)alkoxy(lower)alkyl;

phenyl(lower)alkyl which has hydroxy(lower)alkyl or  
morpholinyl(lower)alkyl;

ar(lower)alkoxycarbonyl;

25 (2-pyridyl)(lower)alkyl which may have 1 to 3  
substituent(s) selected from the group consisting  
of lower alkyl, lower alkoxy, lower alkoxycarbonyl,  
mono(or di or tri)halo(lower)alkyl and halogen;  
(3-pyridyl)propyl which may have lower alkoxy or  
amino;30 (3-pyridyl)butyl which may have lower alkoxy or  
amino;pyridyl(lower)alkenyl which may have lower alkoxy  
or amino;

35 (2-pyridyl)(lower)alkynyl which may have 1 to 3

5           substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, lower alkoxy carbonyl, mono(or di or tri)halo(lower)alkyl and halogen; (3-pyridyl)(lower)alkynyl which may have lower alkoxy or amino;

10           pyridyl, thiazolyl, imidazolyl or pyrazolyl, each of which may have substituent(s); imidazolyl(lower)alkyl which may have 1 or 2 substituent(s) selected from the group consisting of lower alkyl, lower alkynyl, ar(lower)alkyl, pyridyl(lower)alkyl, mono(or di or tri)halo(lower)alkyl and halogen;

15           pyrazolyl(lower)alkyl which may have hydroxy(lower)alkyl, carboxy(lower)alkyl, lower alkoxy carbonyl(lower)alkyl, morpholinyl(lower)alkyl or morpholinyl carbonyl(lower)alkyl; thiazolyl(lower)alkyl which may have lower alkyl; piperidyl(lower)alkyl which may have hydroxy(lower)alkyl or lower alkoxy;

20           morpholinyl(lower)alkyl which has 1 or 2 substituent(s) selected from the group consisting of ethyl, hydroxy(lower)alkyl, halo(lower)alkyl and lower alkoxy(lower)alkyl; morpholinyl(lower)alkyl which has lower alkyl and lower alkoxy(lower)alkyl;

25           (3,5-dimethylmorpholino)(lower)alkyl; morpholino(lower)alkenyl which may have lower alkyl or lower alkoxy(lower)alkyl;

30           (2- or 3-morpholinyl)(lower)alkenyl which may have lower alkoxy carbonyl; pyrrolidinyl(lower)alkynyl which may have lower alkoxy(lower)alkyl;

35           morpholinyl(lower)alkynyl which may have 1 or 2 substituent(s) selected from the group consisting of ethyl, propyl, isopropyl, isobutyl,

spirocyclo(lower)alkyl, lower alkoxy(lower)alkyl,  
hydroxy(lower)alkyl, carboxy(lower)alkyl,  
di(lower alkyl)carbamoyl, lower alkoxycarbonyl and  
halo(lower)alkyl;

5 morpholinyl(lower)alkynyl which has methyl and  
lower alkoxy;

(dimethylmorpholino)(lower)alkynyl;  
homomorpholinyl(lower)alkynyl which have halogen;  
(morpholinylamino)propyl which may have lower  
10 alkanoyl;

thiomorpholinyl(lower)alkynyl which may have  
substituent(s);

homomorpholinylamino(lower)alkyl;  
thiomorpholinylamino(lower)alkyl; or  
15 saturated heterocyclicimino(lower)alkyl,  
saturated heterocyclicaminocarbonyl(lower)alkyl or  
saturated heterocyclic(lower)alkoxy(lower)alkyl,  
each of which may have substituent(s),

provided that when

20  $R^4$  is 2-[N-methyl-N-(3-pyridylmethyl)amino]ethyl,  
3-(3-pyridyl)propyl,  
3-(3-pyridyl)-2-propynyl,  
4-[(2-methoxymethyl)pyrrolidino]-2-butynyl,  
4-thiomorpholino-2-butynyl,  
25 3-(morpholinoamino)propyl,  
4-morpholino-2-butenyl,  
4-morpholino-2-butynyl, or  
4-(3,3-dimethylmorpholino)-2-butynyl, then  
 $R^1$  is not 3,5-bis(trifluoromethyl)phenyl,

30 and a salt thereof.

2. The compound of claim 1, in which

$Y$  is lower alkylene,

$R^1$  is  $C_6-C_{10}$  aryl which may have 1 or 2 substituent(s)  
35 selected from the group consisting of mono(or di

or tri)halo(lower)alkyl, halogen, lower alkylamino, di(lower)alkylamino and nitro,

5       $R^2$  is  $C_6$ - $C_{10}$  aryl or indolyl, each of which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, mono(or di or tri)halo(lower)alkyl, lower alkylenedioxy, hydroxy, hydroxy(lower)alkyl, lower alkoxy, lower alkylamino and di(lower)alkylamino,

10      $R^3$  is hydrogen, and

10      $R^4$  is pyridyl(lower)alkylamino(lower)alkynyl; (2-pyridyl)propyl which may have 1 to 3 substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, lower alkoxy carbonyl, mono(or di or tri)halo(lower)alkyl and halogen; pyridyl, thiazolyl, imidazolyl or pyrazolyl, each of which may have 1 or 2 substituent(s) selected from the group consisting of lower alkyl, ar(lower)alkyl and pyridyl(lower)alkyl;

15     imidazolyl(lower)alkyl which has 1 or 2

20     substituent(s) selected from the group consisting of lower alkyl, lower alkynyl, ar(lower)alkyl, pyridyl(lower)alkyl, mono(or di or tri)halo(lower)alkyl and halogen;

25     (2-methyl-1H-imidazol-4-yl)(lower)alkyl which has 1 or 2 substituent(s) selected from the group consisting of isopropyl, lower alkynyl,

30     ar(lower)alkyl, pyridyl(lower)alkyl, mono(or di or tri)halo(lower)alkyl and halogen;

30     (5-methyl-1H-imidazol-4-yl)(lower)alkyl which has 1 or 2 substituent(s) selected from the group consisting of isopropyl, lower alkynyl,

35     ar(lower)alkyl, pyridyl(lower)alkyl, mono(or di or tri)halo(lower)alkyl and halogen;

35     piperidyl(lower)alkyl which may have hydroxy(lower)alkyl or lower alkoxy;

5 morpholinyl(lower)alkyl which has 1 or 2  
substituent(s) selected from the group consisting  
of ethyl, hydroxy(lower)alkyl, halo(lower)alkyl and  
lower alkoxy(lower)alkyl;

10 5 morpholinyl(lower)alkyl which has lower alkyl and  
lower alkoxy(lower)alkyl;  
(3,5-dimethylmorpholino)(lower)alkyl;  
morpholino(lower)alkenyl which may have lower alkyl  
or lower alkoxy(lower)alkyl;

15 (2- or 3-morpholinyl)(lower)alkenyl which may have  
lower alkoxy carbonyl;  
pyrrolidinyl(lower)alkynyl which may have lower  
alkoxy(lower)alkyl;

20 morpholinyl(lower)alkynyl which may have 1 or 2  
substituent(s) selected from the group consisting  
of ethyl, propyl, isopropyl, isobutyl,  
spirocyclo(lower)alkyl, lower alkoxy(lower)alkyl,  
hydroxy(lower)alkyl, carboxy(lower)alkyl, di(lower  
alkyl)carbamoyl, lower alkoxy carbonyl and  
halo(lower)alkyl;

25 morpholinyl(lower)alkynyl which has methyl and  
lower alkoxy(lower)alkyl;  
(dimethylmorpholino)(lower)alkynyl; or  
homomorpholinyl(lower)alkynyl which may have  
halogen.

3. The compound of claim 2, in which  
Y is lower alkylene,  
R<sup>1</sup> is phenyl which has 1 or 2 substituent(s) selected  
from the group consisting of trihalo(lower)alkyl,  
halogen, lower alkylamino, di(lower)alkylamino and  
nitro,

35 R<sup>2</sup> is phenyl or indolyl, each of which have 1 or 2  
substituent(s) selected from the group consisting  
of lower alkyl, trihalo(lower)alkyl, lower

alkylenedioxy, hydroxy, hydroxy(lower)alkyl, lower alkoxy, lower alkylamino and di(lower)alkylamino,

5 R<sup>3</sup> is hydrogen, and

R<sup>4</sup> is (2-pyridyl)propyl which may have 1 to 3

10 substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, mono(or di or tri)halo(lower)alkyl and halogen;

15 morpholinyl(lower)alkyl which has 1 or 2 substituent(s) selected from the group consisting of ethyl, hydroxy(lower)alkyl, halo(lower)alkyl and lower alkoxy(lower)alkyl;

20 morpholinyl(lower)alkynyl which may have 1 or 2 substituent(s) selected from the group consisting of ethyl, propyl, isopropyl, isobutyl, spirocyclo(lower)alkyl, lower alkoxy(lower)alkyl, hydroxy(lower)alkyl, carboxy(lower)alkyl, di(lower alkyl)carbamoyl, lower alkoxy carbonyl and halo(lower)alkyl.

25 4. A compound of claim 3, which is selected from the group consisting of

- (1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[4-((3S)-3-ethylmorpholino)-2-butynyl]-2-[(1H-indol-3-yl)methyl]piperazine,
- (2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[2-((2S)-2-methoxymethyl-morpholino)ethyl]piperazine,
- (3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[2-((3R)-3-methoxymethyl-morpholino)ethyl]piperazine,
- (4) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[2-((2R)-2-methoxymethyl-morpholino)ethyl]piperazine,
- (5) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1H-indol-3-yl)methyl]-4-[2-((2S)-2-methoxymethyl-

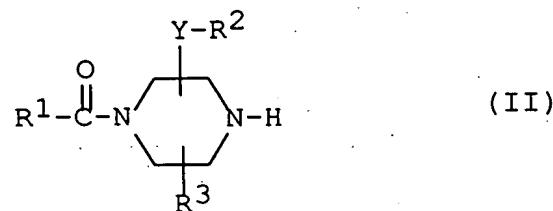
morpholino)ethyl]piperazine, and

(6) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-((3R)-3-ethylmorpholino)ethyl]-2-[(1H-indol-3-yl)-methyl]piperazine

5 or a pharmaceutically acceptable salt thereof.

5. A process for the preparation of the compound of claim 1 or a salt thereof, which comprises,

10 (1) reacting a compound of the formula (II) :



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and Y are each as defined in claim 1, or a salt thereof, with a compound of the formula

20 (III) :

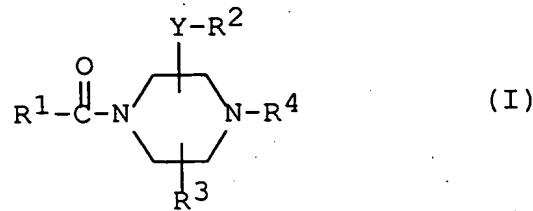


wherein R<sup>4</sup> is as defined in claim 1 and

25 W<sub>1</sub> is a leaving group,

or a salt thereof to give a compound of the formula

(I) :

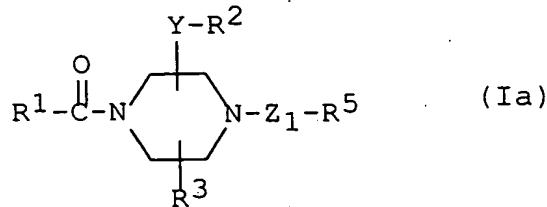


35 wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and Y are each as defined in

claim 1, or a salt thereof,

(2) subjecting a compound of the formula (Ia) :

5



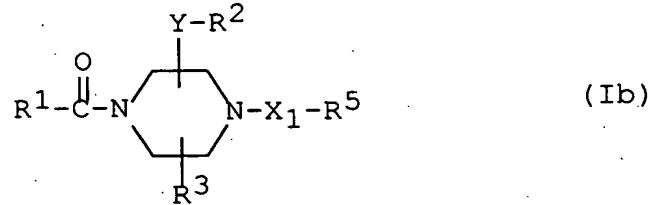
10

wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and Y are each as defined above,  
 R<sup>5</sup> is 2-pyridyl which may have 1 to 3  
 substituent(s) selected from the group  
 consisting of lower alkyl, lower alkoxy,  
 15 lower alkoxy carbonyl, mono(or di or  
 tri)halo(lower)alkyl and halogen; or  
 3-pyridyl which may have lower alkoxy or  
 amino, and

Z<sub>1</sub> is lower alkynylene,

20 or a salt thereof to a reduction reaction to give a  
 compound of the formula (Ib) :

25



30

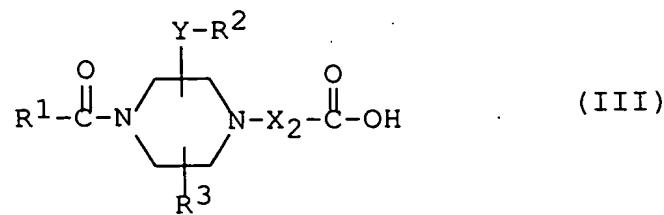
wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, Y and R<sup>5</sup> are each as defined above,  
 and

X<sub>1</sub> is lower alkylene,  
 or a salt thereof,

(3) reacting a compound of the formula (III) :

35

5



10

wherein  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$  and  $\text{Y}$  are each as defined above,  
and

15

$\text{X}_2$  is lower alkylene,  
or its reactive derivative at the carboxy group or a  
salt thereof with a compound of the formula (V) :



20

wherein  $\text{R}^6$  is saturated heterocyclic which may have  
substituent(s),  
or a salt thereof to give a compound (Ic) :

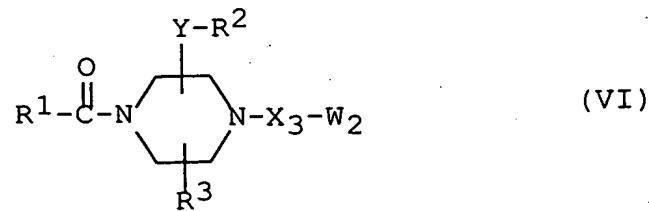
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wherein  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^6$ ,  $\text{X}_2$  and  $\text{Y}$  are each as defined  
above,

30

(4) reacting a compound of the formula (VI) :

35



wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $Y$  are each as defined above,

$X_3$  is lower alkylene and

$W_2$  is a leaving group,

or a salt thereof with a compound of the formula

5 (VII) :

$H-R^7$  (VII)

wherein  $R^7$  is pyridyl(lower)alkylamino;

N-(lower alkyl)-N-[pyridyl(lower)alkyl]-  
amino;

10 1-imidazolyl which may have 1 or 2  
substituent(s) selected from the group  
consisting of lower alkyl, lower alkynyl,  
ar(lower)alkyl, pyridyl(lower)alkyl,  
mono(or di or tri)halo(lower)alkyl and  
halogen;

15 1-pyrazolyl which may have  
hydroxy(lower)alkyl, carboxy(lower)alkyl,  
lower alkoxy carbonyl(lower)alkyl,  
morpholinyl(lower)alkyl or  
morpholinyl carbonyl(lower)alkyl;

20 piperidino which may have  
hydroxy(lower)alkyl or lower alkoxy;  
morpholino which has 1 or 2  
substituent(s) selected from the group  
consisting of ethyl, hydroxy(lower)alkyl,  
halo(lower)alkyl and lower alkoxy-  
(lower)alkyl;

25 morpholino which has lower alkyl and  
lower alkoxy(lower)alkyl;

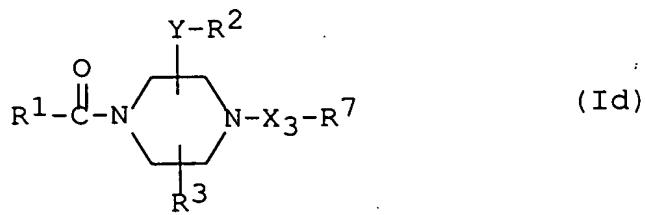
30 3,5-dimethylmorpholino;

morpholinylamino which may have lower  
alkanoyl;

homomorpholinylamino; or  
thiomorpholinylamino,

35 or a salt thereof to give a compound of the formula

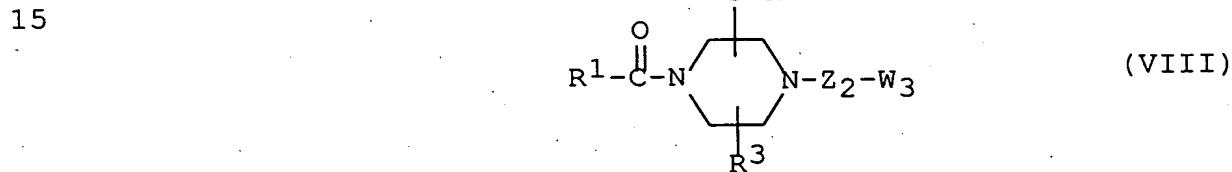
(Id) :



wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^7$ ,  $X_3$  and  $Y$  are each as defined above,

10 or a salt thereof,

(5) reacting a compound of the formula (VIII) :



20 wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $Y$  are each as defined above,  
 $Z_2$  is lower alkenylene, and  
 $W_3$  is a leaving group,

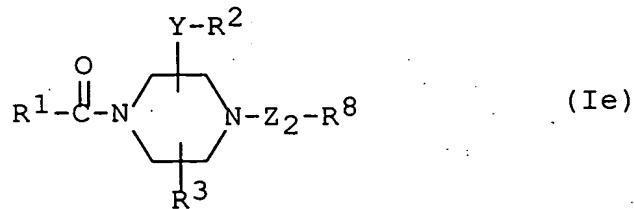
or a salt thereof with a compound of the formula (IX) :



wherein  $R^8$  is morpholino which may have lower alkyl or lower alkoxy(lower)alkyl,

or a salt thereof to give a compound of the formula

30 (Ie) :

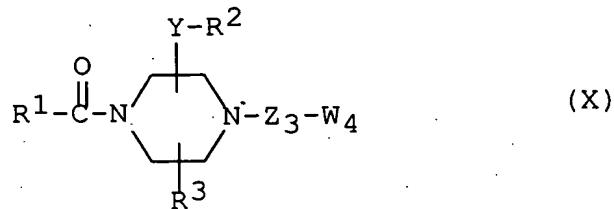


wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^8$ ,  $Y$  and  $Z_2$  are as defined as above,

or a salt thereof,

5 (6) reacting compound of the formula (X) :

10



wherein  $R^1$ ,  $R^2$ ,  $R^3$  and  $Y$  are each as defined above,

15

$Z_3$  is a lower alkynylene and

$W_4$  is a leaving group,

or a salt thereof with a compound of the formula (XI) :

20



25

wherein  $R^9$  is pyrrolidino which may have lower alkoxy(lower)alkyl; morpholino which may have 1 or 2 substituent(s) selected from the group consisting of ethyl, propyl, isopropyl, isobutyl, spirocyclo(lower)alkyl, lower alkoxy(lower)alkyl, hydroxy(lower)alkyl, carboxy(lower)alkyl, di(lower alkyl)carbamoyl, lower alkoxy carbonyl and halo(lower)alkyl;

30

morpholino which has methyl and lower alkoxy;

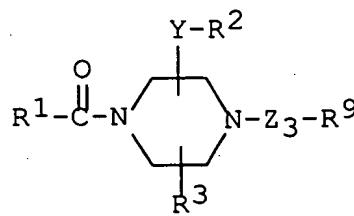
dimethylmorpholino; or

homomorpholino which has halogen,

35

or a salt thereof to give a compound of the formula

(If) :



wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^9$ ,  $Y$  and  $Z_3$  are each as defined  
10 above,  
or a salt thereof.

15

6. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.
7. A compound of claim 1 for use as a medicament.
- 20 8. A method for treating or preventing Tachykinin-mediated diseases which comprises administering an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof to human being or animals.
- 25 9. A compound of claim 1 for use as Tachykinin antagonist.
10. Use of a compound of claim 1 for manufacture of a medicament for treating or preventing Tachykinin-mediated diseases.

30